Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1379422

Anatolian Curr Med J. 2024;6(1):29-37

Clinical profiles in pediatric systemic lupus erythematosus: a retrospective study

Aylin Kılınç Uğurlu[1], Sare Gülfem Özlü[2], Evrim Kargın Çakıcı[2], Özlem Aydoğ[2], Gülay Demircin[3], Ayşe Öner[4], Mehmet Bülbül[2]

[1]Department of Pediatrics, Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Ankara, Turkiye
[2]Department of Pediatric Nephrology, Dr. Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital, Ankara, Turkiye
[3]TOBB ETU Hospital, Department of Pediatric Nephrology, Ankara, Turkiye
[4]Division of Pediatric Nephrology, Department of Pediatrics, Faculty of Medicine, Maltepe University, İstanbul, Turkiye

Cite this article as: Kılınç Uğurlu A, Gülfem Özlü S, Kargın Çakıcı E, et al. Clinical profiles in pediatric systemic lupus erythematosus: a retrospective study. *Anatolian Curr Med J.* 2024;6(1):29-37.

Received: 22.10.2023 ◆ **Accepted**: 06.12.2023 ◆ **Published**: 15.01.2024

ABSTRACT

Aims: This study aimed to analyse clinical and laboratory findings, prognosis, and survival of systemic lupus erythematosus (SLE) patients, differentiating according to gender, pubertal status, and renal involvement.

Methods: Ninety-six pediatric SLE patients, diagnosed using ACR criteria, were retrospectively analyzed. Inclusion criteria comprised age under 18, meeting at least four ACR criteria, and six months of monitoring. Data encompassed demographics, symptoms, diagnosis, organ involvement, autoantibodies, treatment, prognosis, and survival. Categorization was based on gender and pubertal status. Renal biopsies followed WHO-ISN classification, with asymptomatic findings termed "silent lupus nephritis." Biopsied patients were divided into proliferative and non-proliferative lupus nephritis categories, excluding irreversible damage cases. Outcomes studied included remission, relapse, end-stage renal failure, and mortality.

Results: Among 96 participants, females constituted 82.3%, males 17.7%, resulting in a female-to-male ratio of 4.6:1. Mean age at diagnosis was 11.9 years, with 37 prepubertal (38.5%) and 59 pubertal (61.5%) cases. Oral-nasal ulcers (p=0.01) were more prevalent in males related to system involvement. Nephrotic syndrome prevalence increased from 21.6% in prepubertal to 44.1% in pubertal cases (p=0.025). Positive Anticardiolipin IgM antibodies decreased from 56.2% in prepubertal to 25.9% in pubertal cases (p=0.047). Type IV lupus nephritis was predominant, followed by Type II, in prepubertal and pubertal groups and both genders. Proliferative lupus nephritis showed higher rates of renal involvement (95.7% vs. 65.6%), nephrotic syndrome (46.8% vs. 21.9%), proteinuria (89.4% vs. 62.5%), hematuria (57.4% vs. 28.1%), elevated creatinine (43.5% vs. 9.7%), and low albumin (67.4% vs. 23.3%). Cases with proliferative lupus nephritis had higher neuropsychiatric involvement (36.2% vs. 12.5%), seizures (25.5% vs. 3.1%, p=0.008), and increased hemolytic anemia rates (78.7% vs. 56.2%, p=0.033). Thirteen had silent lupus nephritis, revealing various types through biopsy. All reported deaths occurred within the first five years, resulting in stable 91% survival rates at 5, 10, and 15 years.

Conclusion: This study provides insights into the clinical, prognostic, and survival characteristics of pediatric systemic lupus erythematosus (SLE), revealing notable patterns related to gender, pubertal development, and renal involvement. There is an association between proliferative lupus nephritis and renal involvement, nephrotic syndrome, and neuropsychiatric symptoms. Significantly, silent lupus nephritis highlights the complex renal implications, necessitating diligent surveillance for prompt intervention.

Keywords: Pediatric systemic lupus erythematosus (SLE), gender, pubertal status, renal involvement, proliferative lupus nephritis, silent lupus nephritis

This study was presented orally at the 8. Erciyes Pediatri Akademisi Kongresi. The congress took place between 12th and 14th May 2022, with our presentation being held on 13th May 2022.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by inflammation that affects multiple systems of the body. Although the exact cause of SLE is unknown, it is believed that autoimmunity is triggered by genetic, hormonal, or environmental factors that stimulate the immune system. The incidence of SLE varies in different populations. In children, the annual incidence is generally reported to range from 0.36 to 0.9 per 100,000.[1] In adults, it has been reported that the annual incidence is in the region of 3%.[1] SLE occurs in 10–17% of cases during childhood[2] and is more common in females and in Asians, African Americans, Hispanics, and Native Americans. The disease typically manifests after puberty. It is rare in children under five years of age. In both childhood and adulthood, the disease incidence is higher in females. The prevalence of SLE is higher in prepubertal girls than in boys, with a ratio of 4:1. However, during the pubertal period, this ratio increases significantly to 8:1.[3] SLE has a variable prognosis and severity. While some cases present with mild generalized symptoms, others may have a severe course with multiple organ involvement. There needs to be more research on how the clinical findings of SLE vary with age, mainly comparing children and adults and insufficient

Corresponding Author: Aylin KILINÇ UĞURLU, aylin@ugurlu.org

This work is licensed under a Creative Commons Attribution 4.0 International License.

studies on the evaluation of disease progression in childhood groups.[4] This study aims to evaluate the clinical and laboratory findings, prognosis, and long-term outcome of childhood SLE cases followed up in our clinic, and to analyze disease characteristics according to sex (male-female), pubertal status (pubertal-prepubertal) and renal biopsy results (proliferative-nonproliferative nephritis).

METHODS

The study was derived from the thesis on "Evaluation of epidemiological characteristics, clinical and laboratory findings, and prognosis of patients with systemic lupus erythematosus observed between 1990 and 2013: a retrospective study" dated 2014 in Ankara Dr Sami Ulus Pediatrics Training and Research Hospital. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study retrospectively analyzed the data of 96 patients diagnosed with systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) criteria,[5] who were monitored for a minimum of 6 months at the Department of Pediatric Nephrology of Dr. Sami Ulus Maternity, Gynecology, Pediatrics Training and Research Hospital. Inclusion criteria comprised patients diagnosed under the age of 18, with at least four of the 11 ACR SLE criteria positive, monitoring for at least six months, and having sufficient records that permit analysis. A uniform form was used to record the gender, age, origin of symptoms, diagnosis date, the ACR SLE criteria at the time of diagnosis, organ involvement, autoantibody and laboratory profiles, treatment received, follow-up, prognosis, causes of death, and survival times of each patient; this form was completed by only one clinician using files and computerized medical records.

This study compared patients based on gender. Patients were segregated based on pubertal status into two categories: prepubertal and pubertal. Prepubertal patients were categorized as Tanner stage 1 upon pubertal examination, whereas pubertal patients were identified as Tanner stage 2 or higher.[6]

Renal biopsy results were classified according to the WHO-International Society of Nephrology revised criteria for lupus nephritis.[7] Cases without clinical evidence of renal involvement but with nephritic findings on biopsy were defined as silent lupus nephritis.

Patients who underwent renal biopsy were classified as having either proliferative or non-proliferative lupus nephritis.[8] Patients with type III and IV lupus nephritis were classified as proliferative, whereas patients with type I, II and V lupus nephritis were classified as non-proliferative. Patients with type VI lupus nephritis and irreversible renal damage were excluded.

The patients had four prognoses: remission, relapse, end-stage renal failure (ESRD), and death. Remission was defined as the stabilization and improvement of renal function for at least 6 months, the disappearance of urinary sediment abnormalities such as hematuria and cellular cilia, a reduction in proteinuria (protein/creatinine ratio of less than 0.2 or protein positive), and the normalization of C3 levels. Relapse was defined as an increase in proteinuria (>960 mg/m^2/day) and/or activation of sediment findings in the urine and/or an increase in creatinine levels after responding to treatment.[9,10] ESRD was defined as the requirement for permanent dialysis.[9,10]

Statistical Analysis

In this study, statistical analysis were performed using SPSS 20.0 software. Kolmogorov Smirnov normality test was used to analyse the conformity to normal distribution and Levene's test statistics was used for the conformity of homogeneous variance assumption. Descriptive statistics of continuous variables were presented as mean ± standard deviation and categorical variables were presented as number of patients (N) and percentage (%). Mann Whitney U test was used to analyse continuous variables for two groups. In the comparison of categorical variables between groups, chi-square test or fisher exact test was used. In addition, Kaplan-Meier curve was used to investigate the effect of survival and renal survival of the patients and renal biopsy classification on the presence of ESRD. Test results were evaluated at a significance level of p=<0.05.

RESULTS

Out of 96 participants enrolled in this research, 79 (82.3% of the total) were identified as female, while 17 (17.7% of the total) were classified as male. The ratio between female and male participants was determined to be 4.6:1. The mean age of the patients at the time of diagnosis was 11.9±3.4 years. The follow-up period was 5.7 (0.5-13) years. Of the patients, 37 (38.5%) were prepubertal, out of which 27 (73%) were girls and 10 (27%) were boys (F/M:2.7:1). Whereas 59 (61.5%) were pubertal, among whom 52 (88.1%) were girls and 7 (11.9%) were boys (F/M: 7.4:1). **Table 1** presents numerical and percentage data on the clinical and laboratory findings, systemic involvement, laboratory results according to the ACR SLE diagnostic criteria, and prognosis of the patients included in the study.

Among the patients in the study, the malar rash was present in 50 (52.1%) individuals, renal involvement in 76 (79.2%), hematologic involvement in 72 (75%), ANA positivity in 87 (90.6%), and anti-dsDNA positivity in 69 (71.9%), based on the ACR SLE diagnostic criteria for clinical and laboratory findings. Patients with cardiac

involvement were most diagnosed with pericarditis, while patients with neuropsychiatric involvement were most diagnosed with seizures. Furthermore, it was observed that individuals exhibiting hematologic involvement were predominantly diagnosed with hemolytic anemia. The clinical presentation indicated a comparatively lower incidence of oral-nasal ulcers. Following our analysis of the patients' prognosis, we found that 63 patients (63.6%) were in remission, 18 (18.2%) had relapsed, 7 (7.1%) had exited, while 11 (11.1%) had developed ESRD.

Table 1. System involvement, laboratory findings and prognosis of patients with SLE

	Total n (%) n: 96 (100%)
Malar rash	50 (52.1%)
Discoid rash	15 (15.6%)
Photosensitivity	13 (13.5%)
Oral-nasal ulcer	11 (11.5%)
Joint involvement	45 (46.9%)
Renal involvement	76 (79.2%)
Proteinuria	71 (74%)
Hematuria	43 (44.8%)
Nephritic syndrome	22 (22.9%)
Nephrotic syndrome	34 (35.4%)
Cellular cylinder	17 (17.7%)
Neuropsychiatric involvement	24 (25%)
Seizure	15 (15.6%)
Psychosis	4 (4.2%)
Headache	5 (5.2%)
Cardiac involvement	16 (16.6%)
Endocarditis	3 (18.8%)
Myocarditis	1 (6.2%)
Pericarditis	12 (75%)
Pleuritis	12 (12%)
Hematologic involvement	72 (75%)
Hemolytic anemia	70 (72.9%)
Leukopenia	30 (31.2%)
Lymphopenia	35 (36.8%)
Thrombocytopenia	16 (16.8%)
ANA	87 (90.6%)
Anti-dsDNA	69 (71.9%)
Anti-smith (n: 72)	6 (8.3%)
Anti-cardiolipin IgM (n: 43)	16 (37.2%)
Anti-cardiolipin IgG (n: 41)	11 (26.8%)
Lupus anticoagulant (n: 15)	6 (40%)
VDRL (n: 60)	4 (6.7%)
Prognosis	
Remission	63 (63.6%)
Relapse	18 (18.2%)
Exitus	7 (7.1%)
ESRD	11 (11.1%)

Male patients showed a higher frequency of oral-nasal ulcers (p=0.01) when compared to female patients, based on their system involvement. **Table 2** provides a comparison of patients' gender with regards to system involvement, laboratory findings, and prognosis.

Table 2. System involvement, laboratory findings and prognosis by gender in patients with SLE

	Total n: 96 (100%)	Male n: 17 (17.7%)	Female n: 79 (82,3%)	p value
Malar rash	50 (52.1%)	11 (64.7%)	39 (49.4%)	0.25
Discoid rash	15 (15.6%)	1 (5.9%)	14 (17.7%)	0.22
Photosensitivity	13 (13.5%)	1 (5.9%)	12 (15.2%)	0.30
Oral-nasal ulcer	11 (11.5%)	5 (29.4%)	6 (7.6%)	**0.010***
Joint involvement	45 (46.9%)	9 (52.9%)	36 (45.6%)	0.58
Renal involvement	76 (79.2%)	14 (82.4%)	62 (78.5%)	0.72
Proteinuria	71 (74%)	14 (82.4%)	57 (72.2%)	0.38
Hematuria	43 (44.8%)	10 (58.8%)	33 (41.8%)	0.20
Nephritic syndrome	22 (22.9%)	3 (17.6%)	19 (24.1%)	0.56
Nephrotic syndrome	34 (35.4%)	7 (41.2%)	27 (34.2%)	0.58
Cellular cylinder	17 (17.7%)	3 (17.6%)	14 (17.7%)	0.99
Neuropsychiatric involvement	24 (25%)	4 (23.5%)	20 (25.3%)	0.87
Seizure	15 (15.6%)	4 (23.5%)	13 (16.4%)	0.32
Psychosis	4 (4.2%)	1 (5.9%)	3 (3.8%)	0.54
Headache	5 (5.2%)	1 (5.9%)	4 (5.1%)	0.63
Cardiac involvement	16 (16.6%)	3 (17.6%)	13 (16.4%)	0.90
Endocarditis	3 (3%)	0 (0.0%)	3 (3.7%)	0.20
Myocarditis	1 (1%)	0 (0.0%)	1 (1%)	0.56
Pericarditis	12 (12.5%)	3 (17.6%)	9 (11%)	0.57
Pleuritis	12 (12%)	4 (23.5%)	8 (10.1%)	0.13
Hematologic involvement	72 (75%)	14 (82.4%)	58 (73.4%)	0.44
Hemolytic anemia	70 (72.9%)	14 (82.4%)	56 (70.9%)	0.33
Leukopenia	30 (31.2%)	7 (41.2%)	23 (29.1%)	0.33
Lymphopenia	35 (36.8%)	7 (41.2%)	28 (35.9%)	0.68
Thrombocytopenia	16 (16.8%)	4 (23.5%)	12 (15.4%)	0.41
ANA	87 (90.6%)	15 (88.2%)	72 (91.1%)	0.70
Anti-dsDNA	69 (71.9%)	14 (82.4%)	55 (69.6%)	0.28
Anti-smith (n: 72)	6 (8.3%)	2 (16.7%)	4 (6.7%)	0.25
Anti-cardiolipin IgM (n: 43)	16 (37.2%)	4 (44.4%)	12 (35.3%)	0.61
Anti-cardiolipin IgG (n: 41)	11 (26.8%)	1 (11.1%)	10 (31.2%)	0.22
Lupus anticoagulant (n: 15)	6 (40%)	1 (50%)	5 (38.5%)	0.65
VDRL (n: 60)	4 (6.7%)	1 (9.1%)	3 (6.1%)	0.56
Prognosis				
Remission	63 (63.6%)	10 (55.6%)	53 (65.4%)	0.43
Relapse	18 (18.2%)	3 (16.7%)	15 (18.5%)	0.85
Exitus	7 (7.1%)	2 (11.1%)	5 (6.2%)	0.46
ESRD	11 (11.1%)	3 (16.7%)	8 (9.9%)	0.40

*The values in bold represent p value < 0.05, ESRD: End-stage renal disease

Nephrotic syndrome was reported to be 21.6% in the prepubertal group, which increased to 44.1% in the pubertal group (p=0.025) when the cases were compared based on pubertal status. The prevalence of positive Anticardiolipin IgM antibodies decreased from 56.2% in the prepubertal group to 25.9% in the pubertal group (p=0.047), as compared based on the patient's pubertal status. A comparison of prognoses based on pubertal status revealed that prepubertal patients had a higher mortality rate, whereas pubertal patients had a higher

rate of end-stage renal disease (p>0.05). The comparison of patients' pubertal status with system involvement, laboratory findings and prognosis are shown in **Table 3**.

Table 3. System involvement, laboratory findings and prognosis of prepubertal and pubertal cases in patients with SLE

	Total n:96 (100%)	Prepubertal n: 37 (38,5%)	Pubertal n: 59 (61,5%)	p value
Malar rash	50 (52.1%)	20 (54.1%)	30 (50.8%)	0.76
Discoid rash	15 (15.6%)	8 (21.6%)	7 (11.9%)	0.20
Photosensitivity	13 (13.5%)	8 (21.6%)	5 (8.5%)	0.06
Oral-nasal ulcer	11 (11.5%)	3 (8.1%)	8 (13.6%)	0.41
Joint involvement	45 (46.9%)	13 (35.1%)	32 (54.2%)	0.06
Renal involvement	76 (79.2%)	26 (70.3%)	50 (84.7%)	0.08
Proteinuria	71 (74%)	25 (67.6%)	46 (78.0%)	0.25
Hematuria	43 (44.8%)	13 (35.1%)	30 (50.8%)	0.13
Nephritic syndrome	22 (22.9%)	7 (18.9%)	15 (25.4%)	0.46
Nephrotic syndrome	34 (35.4%)	8 (21.6%)	26 (44.1%)	**0.025***
Cellular cylinder	17 (17.7%)	5 (13.5%)	12 (20.3%)	0.39
Neuropsychiatric involvement	24 (25%)	10 (27.0%)	14 (23.7%)	0.71
Seizure	15 (15.6%)	8 (21.6%)	9 (15.3%)	0.89
Psychosis	4 (4.2%)	1 (2.7%)	3 (5.1%)	0.49
Headache	5 (5.2%)	1 (2.7%)	4 (6.8%)	0.35
Cardiac involvement	16 (16.6%)	6 (16%)	10 (16.9%)	0.92
Endocarditis	3 (3%)	2 (5.4%)	1 (1.6%)	0.76
Myocarditis	1 (1%)	1 (2.7%)	0 (0%)	0.20
Pericarditis	12 (12.5%)	3 (8%)	9 (15.2%)	0.16
Pleuritis	12 (12.5%)	3 (8.1%)	9 (15.3%)	0.13
Hematologic involvement	72 (75%)	27 (73%)	45 (76.3%)	0.71
Hemolytic anemia	70 (72.9%)	26 (70.3%)	44 (74.6%)	0.64
Leukopenia	30 (31.2%)	12 (32.4%)	18 (30.5%)	0.84
Lymphopenia	35 (36.8%)	13 (35.1%)	22 (37.9%)	0.78
Thrombocytopenia	16 (16.8%)	8 (21.6%)	8 (13.8%)	0.32
ANA	87 (90.6%)	33 (89.2%)	54 (91.5%)	0.70
Anti-dsDNA	69 (71.9%)	28 (75.7%)	41 (69.5%)	0.51
Anti-smith (n: 72)	6 (8.3%)	3 (9.7%)	3 (7.3%)	0.52
Anti-cardiolipin IgM (n: 43)	16 (37.2%)	9 (56.2%)	7 (25.9%)	**0.047***
Anti-cardiolipin IgG (n: 41)	11 (26.8%)	4 (25%)	7 (28%)	0.83
Lupus anticoagulant (n: 15)	6 (40%)	3 (50%)	3 (33.3%)	0.45
VDRL (n: 60)	4 (6.7%)	2 (7.4%)	2 (6.1%)	0.61
Prognosis				
Remission	63 (63.6%)	23 (59%)	40 (66.7%)	0.43
Relapse	18 (18.2%)	9 (23.1%)	9 (15%)	0.30
Exitus	7 (7.1%)	4 (10.3%)	3 (5%)	0.27
ESRD	11 (11.1%)	3 (7.7%)	8 (13.3%)	0.38

*The values in bold represent p value < 0.05, ESRD: End-stage renal disease

Ten out of the 96 patients involved in our study were not eligible for a biopsy for various reasons, such as a disorder in their bleeding profile. Only three of the 86 patients who underwent a biopsy had renal biopsy results reported as insufficient due to inadequate material. Of 83 patients, 51% were diagnosed with type IV lupus nephritis, followed by 30% with Type II, 7% with type V, 6% with Type III, 5% with type VI and 1% with Type I. In both prepubertal and pubertal groups and across both genders, type IV lupus nephritis was the most common Type, followed by Type II as the second most common Type.

Based on biopsy results, we divided our patients into those with proliferative lupus nephritis and those with nonproliferative lupus nephritis. We excluded four cases with lupus nephritis of type VI on biopsy. Among our patients (n:79), 59% (n:47) had proliferative lupus nephritis. 41% (n:32) had nonproliferative lupus nephritis. Within the proliferative group, 6% (n:5) had Type III, and 53% (n:42) had Type IV. Meanwhile, within the nonproliferative group, 1% (n:1) had Type I, 39% (n:25) had Type II, and 6% (n:6) had Type V lupus nephritis.

The rate of renal involvement in proliferative lupus nephritis was 95.7% compared to 65.6% in nonproliferative lupus nephritis (p=0.001); the rate of nephrotic syndrome was 46.8% compared to 21.9% in nonproliferative lupus nephritis (p=0.024); the rate of proteinuria was 89.4% compared to 62.5% in nonproliferative lupus nephritis (p=0.004); hematuria was 57.4% compared to 28.1% in nonproliferative lupus nephritis (p=0.01); elevated creatinine at first presentation was 43.5% compared to 9.7% in nonproliferative lupus nephritis (p=0.001); low albumin at first presentation was 67.4% compared to 23.3% in nonproliferative lupus nephritis (p=0.001) (**Table 4**).

The rate of neuropsychiatric involvement was 36.2% in the proliferative group compared to 12.5% in non-proliferative lupus nephritis (p=0.019); the rate of seizures was 25.5% compared to 3.1% in non-proliferative lupus nephritis (p=0.008). Neuropsychiatric involvement was present in 17 cases of proliferative lupus nephritis, with seizures in 12, psychosis in 3, and headache in 3. Neuropsychiatric involvement was present in 4 cases of nonproliferative lupus nephritis. Of these patients, 1 had a seizure, one had a central nervous system hemorrhage, 1 had a central nervous system infarction, and 1 had chorea. Cranial magnetic resonance imaging appeared compatible with vasculitis in 3 of our patients. The rate of hemolytic anemia was 78.7% in proliferative lupus nephritis and 56.2% in non-proliferative lupus nephritis (p=0.033) (**Table 4**).

In our study, 66 out of 79 patients in this group had evidence of renal involvement. The remaining 13 (12%) patients had no clinical or laboratory evidence of renal involvement. However, when we analysed the biopsies of these patients, we found one patient each with type I, III and IV lupus nephritis and 10 (50%) patients with type II lupus nephritis. As a result, we found silent lupus nephritis in 13 patients. The comparison of proliferative and non-proliferative lupus nephritis and system involvement, laboratory findings, prognosis and hypertension is shown in **Table 4**.

Table 4. System involvement, laboratory findings, hypertension and prognosis in patients with proliferative and nonproliferative lupus nephritis

	Total n: 79 (100%)	Proliferative n: 47 (59%)	Non-proliferative n: 32(47%)	p value
Gender				
Male	14 (17.7%)	9 (19.2%)	5 (15.6%)	0.68
Female	65 (82.3%)	38 (80.8%)	27 (84.4%)	
Malar rash	43 (54.4%)	28 (59.6%)	15 (46.9%)	0.26
Discoid rash	14 (17.7%)	6 (12.8%)	8 (25%)	0.16
Photosensitivity	13 (16.5%)	7 (14.9%)	6 (18.8%)	0.65
Oral-nasal ulcer	10 (12.7%)	7 (14.9%)	3 (9.4%)	0.46
Joint involvement	40 (50.6%)	25 (53.2%)	15 (46.9%)	0.58
Renal involvement	66 (83.5%)	45 (95.7%)	21 (65.6%)	**0.001***
Proteinuria	62 (78.5%)	42 (89.4%)	20 (62.5%)	**0.004***
Hematuria	36 (45.6%)	27 (57.4%)	9 (28.1%)	**0.010***
Nephritic syndrome	17 (21.5%)	12 (25.5%)	5 (15.6%)	0.29
Nephrotic syndrome	29 (36.7%)	22 (46.8%)	7 (21.9%)	**0.024***
Cellular cylinder	15 (19%)	11 (23.4%)	4 (12.5%)	0.22
Neuropsychiatric involvement	21 (26.5%)	17 (36.2%)	4 (12.5%)	**0.019***
Seizure	13 (16.4%)	12 (25.5%)	1 (3.1%)	**0.008***
Psychosis	3 (3.7%)	3 (6.4%)	0 (0%)	0.20
Headache	3 (3.7%)	3 (6.4%)	0 (0%)	0.20
Cardiac involvement	16 (20.2%)	8 (17%)	10 (31%)	0.58
Endocarditis	2 (2%)	1 (2%)	1 (3%)	
Myocarditis	1 (1%)	1 (2%)	0 (0%)	
Pericarditis	9 (11.3%)	6 (12.7%)	3 (9.3%)	
Pleuritis	10 (12.7%)	8 (17%)	2 (6.3%)	0.15
Hematologic involvement	57 (72.2%)	37 (78.7%)	20 (62.5%)	0.11
Hemolytic anemia	55 (69.6%)	37 (78.7%)	18 (56.2%)	**0.033***
Leukopenia	23 (29.1%)	14 (29.8%)	9 (28.1%)	0.87
Lymphopenia	27 (34.6%)	17 (37%)	10 (31.2%)	0.60
Thrombocytopenia	9 (11.5%)	6 (13%)	3 (9.4%)	0.61
ANA	71 (89.9%)	42 (89.4%)	29 (90.6%)	0.58
Anti-dsDNA	57 (72.2%)	37 (78.7%)	20 (62.5%)	0.11
Anti-smith (n: 59)	4 (6.8%)	2 (5.4%)	2 (9.1%)	0.47
Anti-cardiolipin IgM (n: 31)	12 (38.7%)	7 (33.3%)	5 (50%)	0.37
Anti-cardiolipin IgG (n: 29)	8 (27.6%)	5 (25%)	3 (33.3%)	0.64
Lupus anticoagulant (n: 7)	1 (14.3%)	1 (25%)	0 (0%)	0.57
VDRL (n: 52)	4 (7.7%)	3 (9.7%)	1 (4.8%)	0.46
Prognosis				
Remission	53 (53.5%)	32 (64%)	21 (65.6%)	0.88
Relapse	16 (16.2%)	8 (16%)	8 (25%)	0.31
Exitus	6 (6.1%)	5 (10%)	1 (3.1%)	0.23
ESRD	7 (7.1%)	5 (10%)	2 (6.3%)	0.43
Hypertension	24 (30.4%)	17 (36.2%)	7 (21.9%)	0.17
C3 impairment (n: 76)	52 (68.4%)	34 (75.6%)	18 (58%)	0.10
C4 impairment (n: 76)	53 (69.7%)	34 (75.6%)	19 (61.3%)	0.18
Creatinine (n: 77)	23 (29.9%)	20 (43.5%)	3 (9.7%)	**0.001***
Albümin (n: 76)	38 (50%)	31 (67.4%)	7 (23.3%)	**0.001***

*The values in bold represent p value < 0.05, ESRD: End-stage renal disease

Among the 79 patients with renal involvement, three individuals were not evaluated for prognosis since they did not receive follow-up treatment at our clinic. Eleven out of 76 patients developed end-stage renal disease while under our care. The analysis of biopsies performed on 11 patients who developed end-stage renal failure, revealed that five of them had Type IV, two had Type V, and four had Type VI lupus nephritis (**Table 4**).

Our study found higher rates of ESRD and mortality in boys compared to girls (p>0.05). Although mortality was higher in the prepubertal period, our patients had a higher incidence of ESRD in the pubertal period (p>0.05). In the analysis of the prognosis of proliferative and nonproliferative lupus nephritis groups, it was found that mortality and end-stage renal disease rates were higher in proliferative lupus nephritis, while the relapse rate was higher in non-proliferative lupus nephritis (p>0.05).

During follow-up, seven patients died. After analyzing the causes of death, we found that one patient died due to macrophage activation syndrome, another patient died due to renal failure, one more patient died due to multiple organ failure, two patients died due to sepsis, and the remaining two patients died at their homes. All reported deaths occurred within the first five years. Consequently, the survival rates of our patients at 5, 10, and 15 years were 91%.

DISCUSSION

Systemic lupus erythematosus is a chronic autoimmune disease that involves inflammation and affects multiple organ systems. Pathogenic autoantibodies and immune complexes are involved in its pathogenesis. The incidence of systemic lupus erythematosus is higher in females both in childhood and in adulthood. The onset of the disease typically occurs after puberty.[11,12] This study examines the complex clinical details, prognosis, and results of pediatric patients suffering from systemic lupus erythematosus (SLE). The research comprehensively evaluates the effect of gender, pubertal status, and renal biopsy outcomes on the symptoms of childhood SLE. The prominence of type IV and II lupus nephritis within the patient cohort is of paramount importance, highlighting their critical role in the course of the disease. The study highlights the critical importance of proliferative lupus nephritis, which is notably linked to renal involvement, nephrotic syndrome, and neuropsychiatric symptoms. A significant discovery has emerged in the diagnosis of lupus nephritis in 16% of individuals without any obvious clinical or laboratory symptoms - silent lupus nephritis. Notably, a significant number of cases with type II lupus nephritis have been detected among these individuals, highlighting the concealed renal impacts that require increased awareness. To mitigate the effects

of this concealed disease, the study emphasizes the need for sustained vigilance and careful monitoring. Prompt intervention and careful management strategies are crucial to effectively address the concealed dimensions of renal involvement in pediatric systemic lupus erythematosus cases.

Our study, consistent with the literature, found that the girl/boy ratio in favour of girls increased as the pubertal period progressed.[13,14] This is thought to be related to hormonal changes, such as an increase in estrogen and progesterone as the pubertal period progresses and the disease gradually acquires adult characteristics.[15]

Renal, hematological and malar rash were the most common systems involved in our patients. Patients with renal involvement were more likely to experience proteinuria, while those with hematological involvement often presented with haemolytic anaemia. Thabet et al.[16] (Tunisia) reported that anaemia was the most common presentation, followed by proteinuria and malar rash (67.6%). Lukic et al.[17] (Croatia) found that the musculoskeletal system was the most commonly involved (80%), while cases with renal involvement most commonly presented with hematuria (58%). Although different frequencies of involved organs/systems have been reported in studies from different countries, renal involvement is generally the most common finding in childhood.[17] These varying frequencies in clinical findings are thought to be the result of genetic, environmental, and racial factors.[18]

Wang's study[19] indicated a significantly higher prevalence of rash and alopecia among females, while our data showed that boys had a higher incidence of oral nasal ulcers compared to girls. Boys had more malar rash, joint involvement, renal involvement, pleuritis and hematological involvement than girls, but the differences were not statistically significant. A study conducted in India reported a higher occurrence of renal involvement in boys (78%) than in girls (46%).[20]

Our analysis of patients in pubertal and prepubertal periods showed a significantly higher probability of nephrotic syndrome during pubertal period and anticardiolipin IgM positivity during prepubertal period. The study conducted by Zhu et al.[4] analyzed SLE cases into 3 groups based on age: preschool (age 1-6 years), school age (age 7-11 years), and adolescent (age 12-18 years) periods. The study found that hepatosplenomegaly and arthritis were more frequent during the preschool period compared to the other age groups. However, there were no differences between the groups in terms of nephrotic syndrome and anticardiolipin antibody positivity. In a study by Chiang et al.[21] SLE cases were grouped into 3 categories according to age: prepubertal (< 8 years), pubertal (8-13 years), and postpubertal (13-18 years) periods. The postpubertal period showed a significant increase in renal involvement, lymphopenia, and low c3 and c4 levels compared to the prepubertal period. Similar to our study, the pubertal period showed a higher frequency of renal involvement. This study did not find any difference in terms of anti-cardiolipin antibody positivity.

Lupus nephritis can present in a variety of forms, ranging from asymptomatic microscopic hematuria to severe proliferative glomerulonephritis, and the different rates of renal involvement found in studies may be related to the different severity of symptoms.[22–24] The most common histopathological subtype present in renal involvement is diffuse proliferative glomerulonephritis, which has the most rapid clinical course.[25] In our study, type IV lupus nephritis was the most frequently observed lupus nephritis, as is consistent with the literature.[19,26–28] Type IV lupus nephritis was observed most frequently in our study, followed by Type II, Type V, Type III, Type VI and Type I lupus nephritis, respectively. Studies conducted in Asia and America have reported that Type II and Type V lupus nephritis are the most common types after Type IV.[26,27]

Renal involvement, neuropsychiatric findings, hemolytic anaemia, elevated creatinine, and low albumin are more common in cases with proliferative lupus nephritis. Proteinuria, hematuria, and nephrotic syndrome are more frequent in the proliferative group of cases with renal involvement, while seizures are more common in cases with neuropsychiatric involvement. The study by Wu et al.[29] found hypertension, low glomerular filtration rate, proteinuria, hematuria, and sterile leukocyturia to be statistically significant in cases with proliferative lupus nephritis.

In a study from our country,[30] patients with proliferative lupus nephritis were found to have elevated basal creatinine levels, significant median daily proteinuria, anti-double-stranded DNA (dsDNA) positivity, reduced C3 and C4 complement levels, and the presence of active urinary sediment. Our findings further delineate the clinical picture, demonstrating that renal involvement, neuropsychiatric symptoms, hemolytic anemia, increased creatinine levels, and decreased serum albumin concentrations are more frequently observed in patients with proliferative forms of the disease. Moreover, proteinuria, hematuria, and nephrotic syndrome are more commonly encountered among those with renal manifestations, while seizures predominate in patients with neuropsychiatric complications. Complementing these observations, Wu et al.[29] identified hypertension, a lower glomerular filtration rate, proteinuria, hematuria, and sterile leukocyturia as significant clinical features in patients with proliferative lupus nephritis.

We analyzed biopsies from 13 patients who had no clinical or laboratory findings indicating renal involvement. We found one patient each with type I, III, and IV lupus nephritis and 10 (76%) patients with type II lupus nephritis. As a result, we found silent lupus nephritis in 16% of our patients with renal involvement, which is a significantly high rate.

In the study by Mannemuddhu[31] of 68 patients, 22 (32%) were identified with Silent Lupus Nephritis (SLN), with Class II Lupus Nephritis (LN) being the most frequently observed subtype in this group, representing 50% (n=11) of the SLN cases. Contrastingly, in our research, SLN was detected in 13 (12%) of our patients, and upon histopathological examination of their renal biopsies, a distribution of LN classes was discerned: one patient with Class I, one with Class III, one with Class IV, and a predominant 76% (n=10) with Class II LN, indicating a higher prevalence of Class II LN in our silent cases than reported in Mannemuddhu's cohort. In Gonzalez-Crespo et al.'s[32] study of 18 silent lupus nephritis cases, type I was found in 9, type II in 6, type IV in 1, and type V in 2. In both Gonzalez-Crespo's study[32] and ours, the majority of cases with silent lupus nephritis showed low-grade involvement according to biopsy results. Nevertheless, these patients can also be diagnosed with advanced lupus nephritis, which is significant in determining the prognosis of the disease. The involvement of the kidneys is a crucial factor in determining the prognosis and treatment of the disease. It is imperative to detect any renal involvement in both confirmed and suspected cases. Our study revealed that cases without any symptoms of kidney involvement may still display advanced histopathology biopsy results. Conversely, cases with kidney involvement may display low-grade lupus nephritis in the renal biopsies. The two above-mentioned scenarios play a crucial role in determining both the treatment protocol and prognosis of patients. These results highlight the need for performing a biopsy on patients diagnosed with SLE, even if renal involvement is not present.

According to Gonzalez-Crespo et al.[32] 3 patients died due to causes unrelated to renal involvement, while 3 patients died after developing ESRD. None of our patients with silent lupus nephritis developed ESRD. However, our analysis of biopsy results revealed cases of type III and IV lupus nephritis in our patients with silent lupus nephritis. It is known that ESRD is more common among patients with these types of nephritis.[32]

Our study found higher rates of ESRD and mortality in boys compared to girls. Although prepubertal mortality rate was higher, ESRD incidents were more frequent during pubertal period in our patients. Previous studies reported higher risk of ESRD in boys. Prognosis analysis revealed that death and ESRD incidence were higher in proliferative lupus nephritis cases, while nonproliferative lupus nephritis cases showed higher relapse rate. Wu et al.[29] found higher death and ESRD incidence in proliferative lupus nephritis and higher renal exacerbation incidence in nonproliferative lupus nephritis, which is similar to our findings.

In our study, the mortality rate was 7.1%, with causes of death encompassing macrophage activation syndrome, renal failure, multiple organ failure, sepsis, and unattended home fatalities; this is in marked variance from Samantha et al.'s[33] findings of a 17.39% mortality rate, predominantly due to septicemia in patients with end-stage renal disease, and Listiyono's study34, which reported a 27% one-year post-diagnosis mortality, primarily due to infections in 8 (34%) out of 23 patients and renal failure in 7 (30%) out of 23 patients.

Limitations

The most significant limitation of our study is that it was a retrospective study. Our study's strengths are that it evaluated the clinical, laboratory, and prognostic features of systemic lupus erythematosus (SLE) during childhood among pubertal status and genders - a topic that is rarely touched upon in the literature. This retrospective study provides a comprehensive insight into the clinical and laboratory characteristics, prognosis and survival of paediatric patients with systemic lupus erythematosus (SLE). The analysis focused on gender, pubertal status and renal involvement, shedding light on key patterns and outcomes. The investigation of lupus nephritis types revealed the predominance of type IV, followed by type II, across gender and pubertal categories. Proliferative lupus nephritis emerged as a significant determinant of clinical manifestations, including renal involvement, nephrotic syndrome, proteinuria and neuropsychiatric symptoms. This finding highlights the importance of identifying lupus nephritis subtypes based on renal biopsy in predicting disease severity and associated complications. Significantly, biopsy analysis revealed the emergence of silent lupus nephritis. This hidden condition encompassed occurrences of type I, III, and IV lupus nephritis, as well as a noteworthy incidence of type II lupus nephritis. These latent occurrences highlight the elusive nature of renal effects in systemic lupus erythematosus. Continued attentiveness and careful monitoring are crucial for prompt detection and management of these hidden processes.

CONCLUSION

Our study has explored the complex realm of pediatric Systemic Lupus Erythematosus (SLE), providing insights into many different aspects of the disease's manifestation, prognosis, and outcomes. The results highlight the significant impact of gender and pubertal state on the progression of SLE, with a higher occurrence in females

and an increase in gender disparity during puberty. The presence of renal involvement, which frequently results in proteinuria, is a characteristic aspect of the condition, necessitating careful monitoring and immediate intervention. In addition, our research underscores the crucial significance of renal biopsy in the diagnosis of lupus nephritis and the classification of its subtypes. Notably, type IV and type II lupus nephritis have been identified as significant factors in the advancement of the disease. The predominance of "silent" lupus nephritis is a noteworthy finding, as it indicates the presence of advanced histological alterations in the absence of clinical symptoms. This discovery underscores the importance of maintaining diligent observation and implementing early management strategies.

Moreover, our study highlights the presence of gender inequalities in the outcomes of systemic lupus erythematosus (SLE), with male patients exhibiting a greater susceptibility to end-stage renal disease and mortality. Although death rates are higher during prepuberty, there is a notable increase in incidence of end-stage renal disease during the pubertal era. The presence of proliferative lupus nephritis has been found to be linked with elevated mortality rates and a greater likelihood of developing end-stage renal disease. Conversely, nonproliferative lupus nephritis has been associated with a higher probability of relapse.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was derived from the thesis on "Evaluation of epidemiological characteristics, clinical and laboratory findings, and prognosis of patients with systemic lupus erythematosus observed between 1990 and 2013: a retrospective study" dated 2014 in Ankara Dr Sami Ulus Pediatrics Training and Research Hospital.

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Acknowledgement

We thank all participants and their families for their involvement in our research.

REFERENCES

1. Bernatsky S, Joseph L, Pineau CA, Tamblyn R, Feldman DE, Clarke AE. A population-based assessment of systemic lupus erythematosus incidence and prevalence—results and implications of using administrative data for epidemiological studies. *Rheumatol.* 2007;46(12):1814-1818.
2. Cassidy JT. Juvenile idiopathic arthritis. In Cassidy JT, Petty R. E. 2005.
3. Salmon J, Pricop L, D'Agati V. Immunopathology of systemic lupus erythematosus. In: Hochberg M, Silman AK, Smolen J, et al. (eds.). Rheumatology. 6th ed. Elsevier Mosby, St Louis 2015:1052-1067.
4. Zhu J, Wu F, Huang X. Age-related differences in the clinical characteristics of systemic lupus erythematosus in children. *Rheumatol Int.* 2013;33(1):111-115.
5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheumatism.* 1997;40(9):1725. doi:10.1002/art.1780400928
6. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291-303.
7. Churg J. Renal disease. *Classific Atlas Glomerular Dis.* 1995:155.
8. Singh S, Saxena R, Palmer BF. Lupus nephritis. *Am J Med Sci.* 2009;337(6):451-460.
9. Mina R, Von Scheven E, Ardoin SP, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. *Arthritis Care Res.* 2012;64(3):375-383.
10. Cattran DC, Feehally J, Terence Cook H, et al. Kidney disease: improving global outcomes (KDIGO) glomerular diseases work group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int.* 2021;100(4S):139-274.
11. Lehman TJA, McCurdy DK, Bernstein BH, King KK, Hanson V. Systemic lupus erythematosus in the first decade of life. *Pediatr.* 1989;83(2):235-239.
12. Smith CD, Cyr M. The history of lupus erythematosus: from Hippocrates to Osler. *Rheumatic Dis Clin North Am.* 1988;14(1):1-14.
13. Pluchinotta FR, Schiavo B, Vittadello F, Martini G, Perilongo G, Zulian F. Distinctive clinical features of pediatric systemic lupus erythematosus in three different age classes. *Lupus.* 2007;16(8):550-555.
14. Bader-Meunier B, Armengaud JB, Haddad E, et al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. *J Pediatr.* 2005;146(5):648-653.
15. Walker SE. Estrogen and autoimmune disease. *Clin Rev Allergy Immunol.* 2011;40(1):60-65.
16. Thabet Y, Mankaï A, Achour A, Sakly W, Trabelsi A, Harbi A. Systemic lupus erythematosus in children: a study about 37 Tunisian cases. *J Clin Cell Immunol.* 2014;5(192):2.
17. Lukic A, Lukic IK, Malcic I, et al. Childhood-onset systemic lupus erythematosus in Croatia: demographic, clinical and laboratory features, and factors influencing time to diagnosis. *Clin Experimen Rheumatol.* 2013;31(5):803-812.
18. Abdwani R, Abdalla E, Al-Zakwani I. Unique characteristics of prepubertal onset systemic lupus erythematosus. *Int J Pediatr.* 2019;2019:9537065.
19. Qiu S, Zhang H, Yu S, et al. Clinical manifestations, prognosis, and treat-to-target assessment of pediatric lupus nephritis. *Pediatr Nephrol.* 2022;37(2):367-376. doi:10.1007/s00467-021-05164-y

20. Nandi M, Mondal R. Renal involvement in childhood lupus: a study from Kolkata, India. *Saudi J Kidney Dis Transplant.* 2012;23(4):871.
21. Chiang LL, Lin YT, Chan HY, Chiang BL. Differential manifestations of prepubescent, pubescent and postpubescent pediatric patients with systemic lupus erythematosus: a retrospective study of 96 Chinese children and adolescents. *Pediatr Rheumatol.* 2012;10(1):1-9.
22. Perfumo F, Martini A. Lupus nephritis in children. *Lupus.* 2005;14(1):83-88.
23. Khandelwal P, Govindarajan S, Bagga A. Management and outcomes in children with lupus nephritis in the developing countries. *Pediatr Nephrol.* 2023;38(4):987-1000. doi:10.1007/s00467-022-05769-x
24. Boussetta A, Louati D, Jellouli M, et al. Lupus nephritis in Tunisian children: predictive factors of poor outcomes. *Saudi J Kidney Dis Transplant.* 2022;33(3):440-448. doi:10.4103/1319-2442.385968
25. Rianthavorn P, Buddhasri A. Long-term renal outcomes of childhood-onset global and segmental diffuse proliferative lupus nephritis. *Pediatr Nephrol.* 2015;30(11):1969-1976.
26. Hui-Yuen JS, Imundo LF, Avitabile C, Kahn PJ, Eichenfield AH, Levy DM. Early versus later onset childhood-onset systemic lupus erythematosus: clinical features, treatment and outcome. *Lupus.* 2011;20(9):952-959.
27. Huang JL, Yeh KW, Yao TC, et al. Pediatric lupus in Asia. *Lupus.* 2010;19(12):1414-1418.
28. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr.* 2008;152(4):550-556.
29. Wu J-Y, Yeh K-W, Huang J-L. Early predictors of outcomes in pediatric lupus nephritis: focus on proliferative lesions. In: Seminars in Arthritis and Rheumatism. Vol 43. Elsevier; 2014:513-520.
30. Duran E, Tolga Y, Taghiyeva A, Bilgin E, Ar M, Ertenli AI. Differences and similarities of proliferative and non-proliferative forms of biopsy-proven lupus nephritis : single centre, cross-disciplinary experience. *Lupus.* 2022;31(9):1147-1156. doi:10.1177/09612033221106305
31. Mannemuddhu SS, Shoemaker LR, Bozorgmehri S, et al. Does kidney biopsy in pediatric lupus patients "complement" the management and outcomes of silent lupus nephritis? lessons learned from a pediatric cohort. *Pediatr Nephrol.* 2023;38(8):2669-2678. doi:10.1007/s00467-022-05859-w
32. González-Crespo MR, López-Fernández JI, Usera G, Poveda MJ, Gómez-Reino JJ. Outcome of silent lupus nephritis. In: Seminars in Arthritis and Rheumatism. Vol 26. Elsevier; 1996:468-476.
33. Samanta M, Nandi M, Mondal R, et al. Childhood lupus nephritis: 12 years of experience from a developing country's perspective. *Eur J Rheumatol.* 2017;4(3):178-183. doi:10.5152/eurjrheum.2017.16117
34. Listiyono F, Murni I, Sumadiono S, Satria C. Predictors of mortality in children with systemic lupus erythematosus. *Paediatr Indonesiana.* 2019;59(1):1-6. doi:10.14238/pi59.1.2019.1-6